UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,090	07/03/2003	Gillian Payne	A-8340	4835

23373 7590 12/20/2005

SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,090	PAYNE ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 6th 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *20-30 and 45-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 31-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03.10.2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-19 and 31-44; and the species of Muc16, cytotoxic agent and the subspecies maytansinoid, in the reply of October 6th 2005 is acknowledged.

2. Claims 20-30 and 45-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply on October 6th 2005.

3. Upon further considerations, **the elections of species as set forth in the restriction/election mailed 09/06/2005 in paragraph 3 is withdrawn for all species**.

4. Claims 1-19 and 31-44 are under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 is indefinite for reciting "functional equivalent" because the exact meaning of the term is not clear. It is not clear what function is being referred in the claim. Is it the antibody binding affinity, avidity or the specificity of the antibody? As

written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. It has been noted that the applicant did not provide the information pertaining to the deposit of the claimed hybridomas (MJ-170, MJ-171, MJ-172 and MJ-173) that produce the claimed antibodies.

Claims 31-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of the claimed hybridomas (MJ-170, MJ-171, MJ-172 and MJ-173). It is not clear that the chimeric hybridomas are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of an antibody is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed monoclonal antibodies, this method will not necessarily reproduce antibodies which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive the antibodies identical to those claimed. Undue experimentation would be

required to screen all of the possible antibody species to obtain the claimed antibodies.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species MJ-170, MJ-171, MJ-172 and MJ-173. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibodies, a suitable deposit is required for patent purposes, evidence of public availability of the claimed MJ-170, MJ-171, MJ-172 and MJ-173 antibodies, or evidence of the reproducibility without undue experimentation of the claimed chimeric antibodies, is required.

Applicant's failure to refer to the deposit information pertaining to the claimed hybridomas (MJ-170, MJ-171, MJ-172 and MJ-173) in the specification is noted and it is required that the required deposit be made and all the conditions of 37 CFR 1.801-

1.809 met.

If the deposit of the claimed hybridomas is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the claimed hybridomas (MJ-170, MJ-171, MJ-172 and MJ-173) has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of the claimed hybridomas (MJ-170, MJ-171, MJ-172 and MJ-173) is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material

will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1 is rejected under 35 U.S.C. 102(b) as anticipated by Radosevich et al (U.S. Patent 6166176; Issue date December 26th, 2000)

Radosevich et al teach monoclonal antibodies to an antigen that is not found in the serum of normal or tumor bearing patients, and is not shed into the culture media by positive cell lines (that is, cancer cells are known to bleb off portions of their cell membranes and release them into the surrounding fluid) (please see brief summary of the invention, in particular).

Thus, Radosevich et al anticipates the antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen, as claimed.

Thus, claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by Radosevich et al.

11. Claims 1, 2, 3 and 9-11 are rejected under 35 U.S.C. 102(b) as anticipated by Hartman et al (Int. J. Cancer 1999; 82:256-267) as evidenced by Zrihan-Licht et al (Eur.

J. Biochem. 1994; 224:787-795) and Parry et al (Biochem, Biophys. Res. Comm. 2001; 283:715-720).

The instant claims are drawn to an isolated monoclonal antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen, an isolated monoclonal antibody that specifically binds to an epitope of a non-shed extracellular portion of a human Muc-1, a hybridoma that produces such antibody, wherein at least a part of said epitope is located within the carboxy-terminal 90 amino acids of the extracellular domain of Muc-1, wherein at least a part of said epitope is located within the amino acid sequence of SEQ ID NO:1, wherein said antibody binds to at least one peptide selected form the group consisting of SEQ ID NOS:8-12

Hartman et al teach monoclonal antibodies that bind a novel protein product of the MUCI gene, MUCI/Y, that is a transmembrane protein, but is devoid of the tandem repeat array (see Figure 1). Hartman et al teach four monoclonal antibodies that bind different epitopes located in the C-terminal 101 amino acids of the MUCI/Y extracellular domain and these C-terminal 101 amino acids are identical to amino acid residues 2 – 65 of SEQ ID NO:1 of the instant application as evidenced by Zrihan-Licht et al and Parry et al. Zrihan-Licht et al teach the sequence of the MUCI/Y protein comprising SEQ ID NO:1 (Figure 3A, residues 77-162), and Parry et al teach the MUC1 proteolytic cleavage sites *in vivo*. Hartman et al teaches that antibody 10D2/36 binds an epitope within residues 47-65 of SEQ ID NO:1 (which is SEQ ID NO:12), antibody 6D3/12 binds an epitope within residues 36-56 of SEQ ID NO:1 and antibodies 6C4/5, 9G2/6 and 7D10/4 bind an epitope within residues 2-21 of SEQ ID NO:1 (see Figure 3). Thus, the

antibodies "10D2/36", "6D3/12" and "6C4/5, 9G2/6, 7D10/4" which binds to an epitope within residues "47-65", "36-56" and "2-21" of SEQ ID NO:1 anticipate the antibody of the instant claims.

Thus, Hartman et al as evidenced by Zrihan-Licht et al and Parry et al anticipate the antibodies, that specifically bind to an epitope of a non-shed extracellular portion of a shed antigen wherein the antigen is human Muc-1, as claimed.

Thus, claims 1, 2, 3 and 9-11 are rejected under 35 U.S.C. 102(b) as anticipated by Hartman et al as evidenced by Zrihan-Licht et al and Parry et al.

12. Claims 1-6 and 9-11 are rejected under 35 U.S.C. 102(e) as anticipated by Kufe et al (U.S. Patent Application Publication 20050053606; Filed 09/11/01).

The instant claims have been described above. The claims further recite an isolated monoclonal antibody wherein said antibody is selected from the group consisting of a recombinant antibody, a fragment of a recombinant antibody, a humanized antibody, wherein said antibody is prepared using a non-shed extracellular portion of the antigen attached to an immunogenic protein carrier and wherein said antibody is produced by immunization of an animal with a recombinant fusion protein comprising an extracellular non-shed portion of the antigen.

Kufe et al teach an extracellular domain "MUC1/ECD", remaining on the cell surface after cleavage of the ectodomain, which typically includes the amino acid sequence comprising SEQ ID NO:1 (which is identical to amino acid residues 35 – 58 of SEQ ID NO:1 of the instant application) (see paragraph 5, in particular). Kufe et al also

teach an antibody that binds to one or more epitopes in the MUC1/ECD sequence SEQ ID NO:1, further that the antibody may be humanized or human monoclonal antibodies (see paragraph 16, in particular) wherein said antibody or fragment thereof is conjugated to a chemotherapeutic agent, radioisotope, toxin, or an effector that induces a cytolytic or cytotoxic immune response (claim 43, in particular). As defined by Kufe et al (paragraph 37), an antibody can include monoclonal (including full length), polyclonal antibodies, multispecific antibodies and antibody fragments, so long as they exhibit the desired biological activity, in addition to the methods of producing an antibody (paragraphs 37-50, in particular).

Thus, the antibody taught by Kufe et al anticipate the antibody as claimed in the instant application that specifically binds to an epitope of a non-shed extracellular portion of a human Muc-1, wherein the epitope consists of SEQ ID NO:1.

Thus claims 1-6 and 9-11 are rejected under 35 U.S.C. 102(e) as anticipated by Kufe et al.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-8 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radosevich et al (U.S. Patent 6166176; Issue date December 26th, 2000) in view of Mack et al (U.S. Publication 20040146862; Filed April 9, 2001) in view of Chari et al (a) (U.S. Patent 6333410, Issued December 25th, 2001) in view of Chari et al (b) (U.S. Paten 6340701, Issued January 22nd, 2000) and in view of Chari et al (c) (U.S. Patent 5846545, Issued December 8th, 1998) and further in view of Ni et al teach (U.S. Patent Publication 20030170237, Filed April 30th, 1998).

Claims have been described supra. The claims further recite an antibody displayed upon the surface of a phage, wherein said fusion protein is a glutathione-S-transferase fusion protein and wherein said antibody is produced by immunization of an animal with a cell expressing a recombinant non-shed extracellular portion of the antigen, further a conjugate comprising an antibody attached to a cytotoxic agent or a prodrug of a cytotoxic agent, wherein the cytotoxic agent is a small drug, wherein said cytotoxic agent is a maytansinoid, taxoid or CC-1065 analog, further a composition comprising the antibody and a pharmaceutically acceptable carrier, a composition comprising a conjugate and a pharmaceutically acceptable carrier

Radosevich et al has been described above. Radosevich et al does not specifically teach that antibody is selected from the group consisting of a recombinant antibody, a fragment of a recombinant antibody, a humanized antibody, wherein said antibody is prepared using a non-shed extracellular portion of the antigen attached to an immunogenic protein carrier and wherein said antibody is produced by immunization of an animal with a recombinant fusion protein comprising an extracellular non-shed

portion of the antigen or a fusion protein with glutathione-S-transferase or the cytotoxic agents as claimed. These deficiencies are made up for by Mack et al, Chari et al (a), Chari et al (b), Chari et al (c) and Ni et al.

Mack et al teach that there are many techniques for the preparation of antibodies e.g., recombinant, monoclonal, polyclonal, in addition to the produce antibodies to the polypeptides of the invention (paragraphs 101 and 193-207, in particular). Further Mack et al teach that transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies, in addition that phage display technology to identify antibodies and heterodimeric Fab fragments that specifically bind to selected antigens. Mack et al also teach an antibody that is conjugated to cytotoxic agent (paragraph 28), or linked to an entirely different molecule which confers new properties to the antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc. (paragraph 102, in particular), and a pharmaceutical composition comprising a pharmaceutically acceptable carrier (paragraph 43, in particular).

Chari et al (a) teach antibody drug-conjugates utilizing Maytansinoids as a conjugate (see brief summary of the invention, in particular).

Chari et al (b) teach cytotoxic agents comprising one or more taxanes linked to an antibody (see brief summary of the invention, in particular). Chari et al (b) also teach (see paragraph 46, in particular) the techniques that allow for the production of extremely specific cell binding agents in the form of specific monoclonal antibodies or fragments thereof, in addition to the techniques for creating monoclonal antibodies, or fragments thereof, by immunizing mice, rats, hamsters, or any other mammal with the

antigen of interest such as the intact target cell, antigens isolated from the target cell, whole virus, attenuated whole virus, and viral proteins such as viral coat proteins. Chari et al (b) teach that sensitized human cells can also be used for the above method and further that another method of creating monoclonal antibodies, or fragments thereof, is the use of phage libraries of sFv (single chain variable region), specifically human sFv.

Chari et al (c) teach cytotoxic agents comprising one or more analogue or derivative of CC-1065 conjugated to an antibody (see brief summary of the invention, in particular).

Ni et al teach (U.S. Patent Publication 20030170237, Filed April 30th, 1998) teach the production of antibodies to extracellular domain of the human G-CSF receptor by directly immunizing the animals using the immunogen, or it can be first fused with a carrier molecule to increase its immunogenicity prior to immunization, and that suitable carrier molecules include peptides include glutathione-S-transferase (paragraph 42, in particular).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to generate an antibody to a non-shed portion of an antigen and a hybridoma that produces the particular antibody because Radosevich et

al teach monoclonal antibodies to an antigen that is not found in the serum of normal or tumor bearing patients, and is not shed into the culture media by positive cell lines (that is, cancer cells are known to bleb off portions of their cell membranes and release them into the surrounding fluid) (please see brief summary of the invention, in particular).

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have used the antibodies of Radosevich et al and combine it with the teachings of Mack et al because Mack et al teach that there are many techniques for the preparation of antibodies e.g., recombinant, monoclonal, polyclonal, in addition to the produce antibodies to the polypeptides of the invention and that transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies, in addition that phage display technology to identify antibodies and heterodimeric Fab fragments that specifically bind to selected antigens., and further because Mack et al also teach an antibody that is conjugated to cytotoxic agent, or linked to an entirely different molecule which confers new properties to the antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.

Moreover, one of ordinary skill in the art would have known to combine the antibodies as taught by Radosevich et al and combine them with the teachings of Chari et al (a), Chari et al (b) and Chari et al (c) because because Chari et al (a) teach antibody drug-conjugates utilizing Maytansinoids as a conjugate, and because Chari et al (b) teach cytotoxic agents comprising one or more taxanes linked to an antibody, and

because Chari et al (c) teach cytotoxic agents comprising one or more analogue or derivative of CC-1065 conjugated to an antibody.

Furthermore, one of ordinary skill in the art would have motivated and would have had a reasonable expectation of success to have used the antibodies of Radosevich et al and combine them with Chari et al (b) and Ni et al because Chari et al (b) teach the techniques that allow for the production of extremely specific cell binding agents in the form of specific monoclonal antibodies or fragments thereof, in addition to the techniques for creating monoclonal antibodies, or fragments thereof, by immunizing mice, rats, hamsters, or any other mammal with the antigen of interest such as the intact target cell, antigens isolated from the target cell, whole virus, attenuated whole virus, and viral proteins such as viral coat proteins, further teaching that sensitized human cells can also be used for the above method and further that another method of creating monoclonal antibodies, or fragments thereof, is the use of phage libraries of sFv (single chain variable region), specifically human sFv and because Ni et al teach the production of antibodies by directly immunizing the animals using the immunogen, or it can be first fused with a carrier molecule to increase its immunogenicity prior to immunization, and that suitable carrier molecules include peptides include glutathione-S-transferase.

Thus it would have been obvious to one skilled in the art to have produced an antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1-11 and 15-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Hartman et al (Int. J. Cancer 1999; 82:256-267) as evidenced by Zrihan-Licht et al (Eur. J. Biochem. 1994; 224:787-795) and Parry et al (Biochem, Biophys. Res. Comm. 2001; 283:715-720) and in view of Mack et al (U.S. Publication 20040146862; Filed April 9, 2001) in view of Chari et al (a) (U.S. Patent 6333410, Issued December 25th, 2001) in view of Chari et al (b) (U.S. Paten 6340701, Issued January 22nd, 2000) and in view of Chari et al (c) (U.S. Patent 5846545, Issued December 8th, 1998) and further in view of Ni et al teach (U.S. Patent Publication 20030170237, Filed April 30th, 1998).

Claims have been described supra.

Hartman et al has been described above. Hartman et al does not specifically teach the recombinant or humanized antibodies or a fusion protein with glutathione-S-transferase or the cytotoxic agents as claimed. These deficiencies are made up for by Mack et al, Chari et al (a), Chari et al (b), Chari et al (c) and Ni et al.

Mack et al has been described above.

Chari et al (a) has been described above.

Chari et al (b) has been described above.

Chari et al (c) has been described above.

Ni et al has been described above.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen, specifically human Muc1 protein.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the monoclonal antibodies as taught by Hartman et al because Hartman et al teach an antibody that bind a novel protein product of the MUCI gene, MUCI/Y, that is a transmembrane protein, but is devoid of the tandem repeat array, in addition to four monoclonal antibodies that bind different epitopes located in the C-terminal 101 amino acids (identical to amino acid residues 2 – 65 of SEQ ID NO:1 of the instant application as evidenced by Zrihan-Licht et al and Parry et al) of the MUCI/Y extracellular domain, which reads on the non-shed extracellular portion of a shed antigen.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have used the antibodies of Hartman et al and combine it with the teachings of Mack et al because Mack et al teach that there are many techniques for the preparation of antibodies e.g., recombinant, monoclonal, polyclonal, in addition to the produce antibodies to the polypeptides of the invention and that transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies, in addition that phage display technology to identify antibodies and heterodimeric Fab fragments that specifically bind to selected

antigens., and further because Mack et al also teach an antibody that is conjugated to cytotoxic agent, or linked to an entirely different molecule which confers new properties to the antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.

Moreover, one of ordinary skill in the art would have known to combine the antibodies as taught by Hartman et al and combine them with the teachings of Chari et al (a), Chari et al (b) and Chari et al (c) because Hartman et al teaches that antibody 10D2/36 binds an epitope within residues 47-65 of SEQ ID NO:1 (which is SEQ ID NO:12), antibody 6D3/12 binds an epitope within residues 36-56 of SEQ ID NO:1 and antibodies 6C4/5, 9G2/6 and 7D10/4 bind an epitope within residues 2-21 of SEQ ID NO:1, and because Chari et al (a) teach antibody drug-conjugates utilizing Maytansinoids as a conjugate, and because Chari et al (b) teach cytotoxic agents comprising one or more taxanes linked to an antibody, and because Chari et al (c) teach cytotoxic agents comprising one or more analogue or derivative of CC-1065 conjugated to an antibody.

Furthermore, one of ordinary skill in the art would have motivated and would have had a reasonable expectation of success to have used the antibodies of Hartman et al and combine them with Chari et al (b) and Ni et al because Hartman et al teach the antibodies "10D2/36", "6D3/12" and "6C4/5, 9G2/6, 7D10/4" which binds to an epitope within residues "47-65", "36-56" and "2-21" of SEQ ID NO:1 and because Chari et al (b) teach the techniques that allow for the production of extremely specific cell binding agents in the form of specific monoclonal antibodies or fragments thereof, in addition to the techniques for creating monoclonal antibodies, or fragments thereof, by immunizing

mice, rats, hamsters, or any other mammal with the antigen of interest such as the intact target cell, antigens isolated from the target cell, whole virus, attenuated whole virus, and viral proteins such as viral coat proteins, further teaching that sensitized human cells can also be used for the above method and further that another method of creating monoclonal antibodies, or fragments thereof, is the use of phage libraries of sFv (single chain variable region), specifically human sFv and because Ni et al teach the production of antibodies by directly immunizing the animals using the immunogen, or it can be first fused with a carrier molecule to increase its immunogenicity prior to immunization, and that suitable carrier molecules include peptides include glutathione-S-transferase.

Thus it would have been obvious to one skilled in the art to have produced an antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen, specifically human Muc1 protein.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1-8 and 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitcham et al (WO 02/06317, International Filing Date July 17th, 2001) as evidenced by the instant specification (page 1, paragraph 3) and as evidenced by Albone et al (U.S. Publication 20050064518, Filed October 16th, 2002) in view of Weiner et al (U.S. Patent 6,512,096 Filed June 25th, 1998) as evidenced by Thorpe et al (U.S. Patent 5,776,427, Issued July 7th, 1998) and in view of Hoogenbooom et al (U.S.

Publication 20030235868, Filed April 22nd, 2002) and in view of Mack et al (U.S. Publication 20040146862; Filed April 9, 2001) in view of Chari et al (a) (U.S. Patent 6333410, Issued December 25th, 2001) in view of Chari et al (b) (U.S. Paten 6340701, Issued January 22nd, 2000) and in view of Chari et al (c) (U.S. Patent 5846545, Issued December 8th, 1998) and further in view of Ni et al teach (U.S. Patent Publication 20030170237, Filed April 30th, 1998).

Claims have been described supra. In addition, the claims recite an isolated antibody as described above wherein at least a part of said epitope is located within the carboxy-terminal 90 amino acids of the extracellular domain of Muc-16, wherein at least a part of said epitope is located within the amino acid sequence of SEQ ID NO:2, wherein said antibody binds to at least one peptide selected form the group consisting of SEQ ID NOS:14-18.

Mitcham et al teach (page 77, in particular) the extracellular part of O772P (which is the same as CA-125 as evidenced by Albone et al in paragraph 0064, and as evidenced by the specification CA-125 and Muc-16 are the same) that is expressed and/or retained on the plasma membrane, making O772P an attracting target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. Mitcham et al also teach the predicted extracellular domain O772P (SEQ ID NO:489, which comprises SEQ ID NO:2 of the instant application), and the proteolytic cleavage site that is likely to occur at position 10 of SEQ ID NO:489. Mitcham et al does not

specifically teach the epitopes that the antibody is directed to or recombinant and humanized antibodies or a fusion protein with glutathione-S-transferase or the cytotoxic agents as claimed. These deficiencies are made up for by Mitcham et al, Weiner et al, Thorpe et al, Hoogenbooom et al, Mack et al, Chari et al (a), Chari et al (b), Chari et al (c) and Ni et al.

Weiner et al teach (paragraphs 16 and detailed description of the preferred embodiment, in particular) a selection method designed to obtain monoclonal antibodies of very high specificity to particular tumor antigens, or to antigenic determinants shared by a single differentiated tissue type and to produce monoclonal antibodies which favor an externally disposed, stable, nonshed antigen. Weiner et al teach that it is important that a stable cell surface antigen be identified for the above method, and the term "stable" means that the target molecule is preferably a constitutive cell membrane glycoprotein integral to the structure and integrity of the membrane, and not a transient resident of the cell which is shed or displaced. Thorpe et al teach antibody-targeting agents having an affinity for antigenic markers found, expressed, accessible on the cell surfaces of tumor associated vascular endothelium as compared to normal vasculature and the antibodies are useful for the treatment and diagnosis of a variety of carcinomas (see column 4 lines 49-61, in particular).

Hoogenboom et al teach (paragraph 6, in particular) that many antibodies to the tumor-associated peptide epitopes of the tandem repeat bind relatively specifically to epithelial tumors and these antibodies against the tandem repeat have different internalization properties and the efficiency of such antibodies is hampered by binding

of the antibody to shed portion of MUC-1 in the serum of the patient, which can cause problems when antibodies are injected intravenously. Hoogenboon et al further teach the formation of large immune complexes between shed portion, with multiple epitopes, and antibodies with one or more binding sites which may lead to the accumulation of complexes in the liver, rapid clearance and toxic side effects associated with this altered pharmacokinetics (e.g. serum sickness). Hoogenbooom et al also teach that if such antibodies are labeled with cytotoxic drugs or radio isotopes, such effects may be detrimental to the antibody's efficacy and therefore antibodies that would not recognize the shed portion but do recognize the remaining portion on the cell surface, would not suffer these therapeutic drawbacks, and could be superior targeting agents. In addition, Hoogenboom et al teach that the disadvantage of many anti-MUC1 antibodies is that they target epitopes that are relatively far removed from the cell surface, reducing the efficacy of natural antibody-mediated immune effectors such as Complement-Dependent Cytotoxicity, and therefore targeting of tumor cells with antibodies to MUC1 epitopes that are more closely located to the cell surface may dramatically increase their anti-tumor cell efficacy.

Mack et al has been described above.

Chari et al (a) has been described above.

Chari et al (b) has been described above.

Chari et al (c) has been described above.

Ni et al has been described above.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen, specifically human Muc-16 protein.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced antibodies against the non-shed extracellular portion of Muc16 by combining the teachings of Mitcham et al and Weiner et al because Mitcham et al teach the extracellular part of O772P that is expressed and/or retained on the plasma membrane, making O772P an attracting target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. In addition Mitcham et al also teach the predicted extracellular domain O772P (SEQ ID NO:489, which comprises SEQ ID NO:2 of the instant application), and the proteolytic cleavage site that is likely to occur at position 10 of SEQ ID NO:489, which reads on the non-shed extracellular portion of a shed antigen, and because Weiner et al teach a selection method designed to obtain monoclonal antibodies of very high specificity to particular tumor antigens, or to antigenic determinants shared by a single differentiated tissue type and to produce monoclonal antibodies which favor an externally disposed, stable, nonshed antigen, and teach that that it is important that a stable cell surface antigen be identified for the above method, wherein the term "stable" means that the target molecule is preferably a constitutive cell membrane glycoprotein integral to the structure and integrity of the membrane, and not a transient resident of the cell which is

shed or displaced, and because Thorpe et al teach antibody-targeting agents having an affinity for antigenic markers found, expressed, accessible on the cell surfaces of tumor associated vascular endothelium as compared to normal vasculature and the antibodies are useful for the treatment and diagnosis of a variety of carcinomas.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to combine the teachings of Mitcham et al and Weiner et al with Hoogenboom et al to produce antibodies against the extracellular epitope of Muc-16 because Hoogenboom et al teach (paragraph 64, in particular) that many antibodies to the tumor-associated peptide epitopes of the tandem repeat bind relatively specifically to epithelial tumors and these antibodies against the tandem repeat have different internalization properties and the efficiency of such antibodies is hampered by binding of the antibody to shed portion of the antigen in the serum of the patient, which can cause problems when antibodies are injected intravenously. Hoogenboon et al further teach the formation of large immune complexes between shed portion, with multiple epitopes, and antibodies with one or more binding sites which may lead to the accumulation of complexes in the liver, rapid clearance and toxic side effects associated with this altered pharmacokinetics (e.g. serum sickness).

Moreover, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to combine the teachings of Mitcham et al, Weiner et al and Hoogenboom et al to produce the antibody wherein at least a part of the epitope is located within the carboxy-terminal 90 amino acids of the extracellular domain of Muc-16, wherein at least a part of epitope is located within the amino acid

sequence of SEQ ID NO:2, wherein said antibody binds to at least one peptide selected form the group consisting of SEQ ID NOS:14-18, because Mitcham et al teach the extracellular sequence of Muc-16 that remains on the cell surface and because Weiner et al teach that it is important that a stable cell surface antigen be identified for the above method, and the term "stable" means that the target molecule is preferably a constitutive cell membrane glycoprotein integral to the structure and integrity of the membrane, and not a transient resident of the cell which is shed or displaced, and because Hoogenboom et al teach that the disadvantage of many anti-MUC1 antibodies is that they target epitopes that are relatively far removed from the cell surface, reducing the efficacy of natural antibody-mediated immune effectors such as Complement-Dependent Cytotoxicity, and therefore targeting of tumor cells with antibodies to MUC1 epitopes that are more closely located to the cell surface may dramatically increase their anti-tumor cell efficacy.

Furthermore, one of ordinary skill in the art would have motivated and would have had a reasonable expectation of success to have combined the teachings of Mitcham et al, Weiner et al and Hoogenboom et al with Mack et al , Chari et al (a), Chari et al (b), Chari et al (c) and Ni et al because Mack et al teach that there are many techniques for the preparation of antibodies e.g., recombinant, monoclonal, polyclonal, in addition to the produce antibodies to the polypeptides of the invention and that transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies, in addition that phage display technology to identify antibodies and heterodimeric Fab fragments that specifically bind to selected antigens., and further

because Mack et al also teach an antibody that is conjugated to cytotoxic agent, or linked to an entirely different molecule which confers new properties to the antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc. and because Chari et al (a) teach antibody drug-conjugates utilizing Maytansinoids as a conjugate, and because Chari et al (b) teach cytotoxic agents comprising one or more taxanes linked to an antibody, and because Chari et al (c) teach cytotoxic agents comprising one or more analogue or derivative of CC-1065 conjugated to an antibody, and because Ni et al teach the production of antibodies by directly immunizing the animals using the immunogen, or it can be first fused with a carrier molecule to increase its immunogenicity prior to immunization, and that suitable carrier molecules include peptides include glutathione-S-transferase.

Thus it would have been obvious to one skilled in the art to have produced an antibody that specifically binds to an epitope of a non-shed extracellular portion of a shed antigen, specifically human Muc16 protein.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claims are allowed

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is

571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER